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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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29 December 1999 (29.12.99)

(54) Title: FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS, AND RELATED METHODS AND DELIVERY SYSTEMS

(57) Abstract

This invention provides folic acid-containing pharmaceutical compositions comprising either an oral contraceptive or a hormone replacement composition. This invention also provides methods of administering folic acid to a subject using the instant pharmaceutical compositions. Finally, this invention provides a drug delivery system useful for administering the instant pharmaceutical compositions.

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 99/08429

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 131 292 A (MORTIMER DR CHRISTOPHER H) 20 June 1984 (1984-06-20) page 1, line 5-35; claims 1-8 page 1, line 57-63 page 2, line 20-34 ---	1-18
X	WO 98 04248 A (ENERGETICS) 5 February 1998 (1998-02-05) page 2-6 page 7, line 3-11 page 10, line 7 - page 11, line 28 page 13, line 25-33 page 18; claims 1,21-23,32; examples ---	3-9, 12-18
X	WO 88 04927 A (DAVIRAND INC) 14 July 1988 (1988-07-14) page 3, line 15-17; claim 1 ---	1,10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 September 1999	16/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 99/08429

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RHODE ET AL: "Effect of Orange Juice, Folic acid, and Oral Contraceptives on Serum Folate in Women taking a Folate-Restricted Diet" J. AM. COLL. NUTR., vol. 2, no. 3, 1983, pages 221-230, XP002114784 the whole document ---	1,2,10, 11
X	BUTTERWORTH ET AL: "Improvement in Cervical Dysplasia Associated with Folic Acid Therapy in Users of Oral Contraceptives" AM. J. CLIN. NUTR., vol. 35, no. 1, 1982, pages 73-82, XP002114785 the whole document ---	1,2,10, 11
X	WHITEHEAD ET AL: "Megaloblastic Changes in the Cervical Epithelium. Association with Oral Contraceptive Therapy and Reversal with Folic acid" J. AMER. MED. ASS., vol. 226, no. 12, 1973, pages 1421-1424, XP002114786 the whole document -----	1,2,10, 11

1

INTERNATIONAL SEARCH REPORT

I. .national application No.
PCT/US 99/ 08429

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 19,20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19, 20

The subject matter of claims 19 and 20 seems to lack an essential feature, in the sense that they concern drug delivery systems for oral contraceptives or hormone replacement compositions. Since the application is directed to the use of folic acid or folate in compositions and methods comprising oral contraceptives or hormone replacement compositions, claims 19 and 20 are clearly outside the scope of the application.
The cited documents in the search report disclose any drug delivery systems with folic acid or folate and oral contraceptives or hormone replacement compositions that the prior art might provide.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 99/08429

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2131292 A	20-06-1984	NONE	
WO 9804248 A	05-02-1998	US 5654011 A	05-08-1997
		US 5807586 A	15-09-1998
		AU 3958797 A	20-02-1998
		EP 0934060 A	11-08-1999
WO 8804927 A	14-07-1988	NONE	

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Published
Without international search report and to be republished upon receipt of that report.

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This invention provides folic acid–containing pharmaceutical compositions comprising either an oral contraceptive or a hormone replacement composition. This invention also provides methods of administering folic acid to a subject using the instant pharmaceutical compositions. Finally, this invention provides a drug delivery system useful for administering the instant pharmaceutical compositions.

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FOLIC ACID-CONTAINING PHARMACEUTICAL COMPOSITIONS, AND RELATED METHODS AND DELIVERY SYSTEMS

Throughout this application, various publications are cited. The disclosure of these publications is hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

Field of the Invention

This invention relates to compositions and methods for delivering folic acid to subjects afflicted with, or at an increased risk of becoming afflicted with, a folic acid-treatable disorder. The folic acid is incorporated into a chronically administered pharmaceutical composition intended for treating or preventing a condition different than the folic acid-treatable disorder.

Background of the Invention

Folic Acid Generally

Folic acid is a vitamin. It plays a crucial role in DNA synthesis, and in hematopoiesis (although the details of this role remain undefined). Folic acid is involved, for example, in single carbon transfers (such as those required for purine and pyrimidine metabolism), and in the re-methylation of homocysteine to methionine.

Folic acid is available, primarily as the polyglutamate, from dietary sources such as whole grains, mushrooms, vegetables, red meat, fish and legumes. Supplementation, however, is provided in the form of the monoglutamate (pteroglutamic acid). Folic acid is absorbed primarily in the proximal small bowel, is highly protein-bound, and is stored in the liver. Almost no unchanged folic acid appears in the urine under normal circumstances, unless excess is provided.

Minimum requirements of folic acid are in the range of 50 µg/day, and increase 3 to 6 times during pregnancy and/or lactation. The U.S. recommended daily allowance for pregnant women is 400 µg/day, and the average pharmacological replacement dose is between 1 and 5 mg/day. Most prenatal vitamins contain 1 mg of folic acid.

The total body store of folic acid is about 5 mg. When a folic acid-deficient patient is treated, reversal of the deficiency begins rapidly (reticulocytosis within 4 days) and resolves within 2 months. If folic acid is administered at a rate of only 50 µg day, assuming no dietary or other intake, signs of folic acid deficiency are manifest after an approximately 3 month lag time. In cases of increased bodily folic acid requirements, such as pregnancy or lactation, this time frame is shortened to 2 to 4 weeks. Fortunately, folic acid supplementation in otherwise healthy young women who have such increased folic acid needs is an accepted practice.

Folic acid has not been reported to cause adverse effects when administered in reasonable, pharmacological doses. The only reported adverse reaction for folic acid

is a decreased level of plasma zinc in the case of prolonged high-dose administration.

Oral Contraceptives and Folic Acid

In pregnant women, correction of low folic acid levels takes at least two months, and reserves can last as little as a few weeks. According to a public health service recommendation, all women who can become pregnant should consume 400 µg/day of folic acid to reduce the risk of birth defects (MMWR Morb Mortal Wkly Rep 1992; 41(RR-14):1-7). Supplementation immediately before discontinuing oral contraceptive use or immediately after positive pregnancy test results may be insufficient to optimally protect the developing fetus.

In addition, multiple studies of women taking oral contraceptives show decreased folic acid levels relative to negative controls. Postulated mechanisms reported for this phenomenon include decreased absorption of polyglutamates, increased excretion of folic acids, increased production of folic acid-binding proteins, and induction of folic acid-dependent hepatic microsomal enzymes.

Decreases of folic acid levels among oral contraceptive users pose an additional risk for such users who become pregnant within three to six months following discontinuation of use.

Disorders and Folic Acid

Numerous disorders can result from insufficient intake of folic acid. Enhanced effects of risk factors for cervical dysplasia (e.g. HPV infection) have been linked to decreased folic acid levels. Sub-optimal body stores of folic acid, as measured by red cell folic acid concentrations, may amplify oncogenic risk. Locally diminished folic acid stores, for example, in cervical tissue, may be a result of oral contraceptive use and are responsible for the dysplastic process. Finally, decreased folic acid levels early in pregnancy are associated with increased birth defects, primarily neural tube defects ("NTD's"). Indeed, randomized control trials of vitamin supplements containing folic acid have shown a dramatic reduction of the incidence of spina bifida and anencephaly.

Administering folic acid can reduce the onset of disorders such as cardiovascular disease and cervical dysplasia. For example, most clinical trials show that high folic acid doses (up to 10 mg/day) have a prophylactic, although not therapeutic, effect against cervical dysplasia (Butterworth, C.E., et al., JAMA (1992) 267(4):528-533; Butterworth C.E., et al., Am J Obstet Gynecol (1992) 166:803-809; Potischman, N. and Brinton, L.A., Cancer Causes and Control (1996) 7:113-126).

As for certain cardiovascular disorders, results from numerous studies indicate that doses of folic acid (1-5 mg/day) reduce elevated levels of homocysteine which can cause such disorders (Boushey, C.J., et al., JAMA (1995) 274:1049-1057); Landgren, F., et al., J Intern Med

(1995) 237:381-388). A single study by Guttormsen (Guttormsen, A.B., et al., J Clin Invest (1996) 98:2174-2183) demonstrated that low-dose folic acid supplementation (200 µg/day) reduces elevated plasma homocysteine levels in patients with intermediate hyperhomocysteinemia (> 40 µmol/L). This reduction is influenced, in part, by the initial causes of hyperhomocysteinemia, i.e., genetic mutation, dietary deficiency and concurrent disease.

Summary of the Invention

This invention provides a pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention also provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a menopausal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the instant

pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a menopausal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a hypogonadal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

Finally, this invention provides a drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, wherein each dosage unit comprises at least one of the instant pharmaceutical compositions.

Detailed Description of the Invention

Definitions

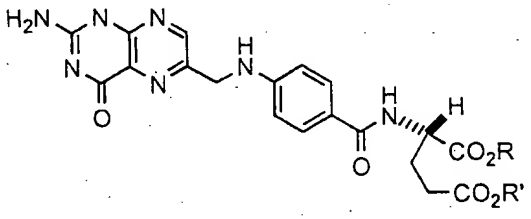
In this invention, certain terms are used which shall have the meanings set forth as follows.

"Androgen-related compound" ("ARC") shall mean a compound which displays an end organ androgen effect. ARC's are exemplified in the Examples below.

"Chronic administration" shall mean administration which occurs either at regular intervals (e.g., daily oral dosage) or continuously (e.g. transdermal delivery for several days) over at least a single time period (e.g., three weeks). The chronic administration can optionally occur over a plurality of time periods.

"Estrogen-related compound" ("ERC") shall mean a compound which displays an end organ estrogen effect. ERC's are exemplified in the Examples below.

"Folic acid" shall mean the compound having the following structure, where R and R' are both H, as well as pharmaceutically acceptable salts and derivatives thereof:



Pharmaceutically acceptable salts are well known in the art and include, without limitation, Na^+, K^+, Mg^{++} and

various amines (Int'l. J. Pharm. (1986) 33:201-217). Pharmaceutically acceptable derivatives are also well known in the art and include, without limitation, esters. Such derivatives are exemplified below.

"Menopausal condition" shall mean a condition that is either a peri-menopausal condition or a post-menopausal condition.

"Menopausal woman" shall mean a woman having an age at which menopause or its onset normally occurs.

"Peri-menopausal condition" shall mean a condition which (i) occurs either during menopausal onset, or prior thereto at a time when menopausal onset normally occurs, and (ii) either is caused by menopausal onset or has a greater than random coincidence therewith. Peri-menopausal conditions include, for example, hot flashes and reduction of bone mass.

"Post-menopausal condition" shall mean a condition which (i) occurs after menopausal onset, and (ii) either is caused by menopause or has a greater than random coincidence therewith. Post-menopausal conditions include, for example, vasomotor symptoms, osteopenia, osteoporosis, cardiovascular disease and cognitive dysfunction.

"Progestin-related compound" ("PRC") shall mean a compound which displays an end organ progestin effect. PRC's are exemplified in the Examples below.

"Subject" shall any animal, such as a primate, mouse, rat, guinea pig or rabbit. In the preferred embodiment, the subject is a human.

Embodiments of the Invention

This invention provides a pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention also provides a method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

Oral contraceptives are widely available commercially, and classifications thereof include, without limitation, progestin only, fixed dose, and phasics. Oral contraceptives routinely contain one or more estrogen-related compounds and progestin-related compounds. Such contraceptives are preferred in this invention and are listed extensively, along with their respective hormone ingredients, in the IPPF Directory of Hormonal Contraceptives. For the purpose of

illustration, selected oral contraceptives and their respective hormone ingredients are listed in the Examples below.

In this embodiment, the disorder can be any folic acid-treatable condition with which pregnant women are afflicted, or to which they are predisposed to become afflicted, at a higher-than-normal incidence. In the preferred embodiment, the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

This invention also provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a menopausal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a menopausal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

The menopausal condition can be a peri-menopausal condition or, alternatively, a post-menopausal condition. Hormonal replacement compositions are widely available commercially, and routinely contain estrogen-related compounds, progestin-related compounds, androgen-related compounds, and others. Such compositions are preferred in this invention and are listed extensively, along with their respective hormone ingredients, in Sturdee, D.W., et al. (Br J Obstet Gynecol (1997) 104:109-115). By way of example, selected hormone replacement compositions and their respective hormone ingredients are listed in the Examples below.

In this embodiment, the disorder can be any folic acid-treatable condition with which menopausal women are afflicted, or to which they are predisposed to become afflicted, at a higher-than-normal incidence. In the preferred embodiment, the disorder is selected from the group consisting of cervical dysplasia, cervical carcinoma and a cardiovascular disorder.

This invention also provides a pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

This invention further provides a method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or

preventing a hypogonadal condition, which comprises administering to the subject the instant pharmaceutical composition, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

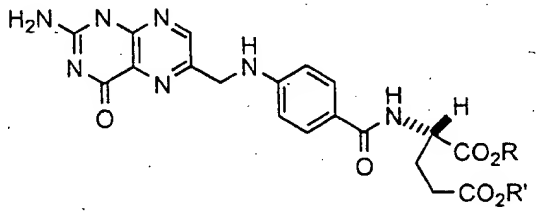
Hormone replacement compositions for hypogonadal conditions routinely contain androgen-related compounds (for male subjects) and estrogen- and progestin-related compounds (for female subjects). Hypogonadal conditions include, by way of example, menopause (with or without reduced libido), Klinefelter's syndrome, and post-orchectomy status. When the subject is female, the disorder can be selected, for example, from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder. When the subject is male, the disorder can be, for example, a cardiovascular disorder.

In this invention, administering the instant pharmaceutical compositions can be effected or performed using any of the various methods and delivery systems known to those skilled in the art. The administering can be performed, for example, intravenously, orally, via implant, transmucosally, transdermally, intramuscularly, and subcutaneously. In addition, the instant pharmaceutical compositions ideally contain one or more routinely used pharmaceutically acceptable carriers. Such carriers are well known to those skilled in the art. The following delivery systems, which employ a number of routinely used carriers, are only representative of the

many embodiments envisioned for administering the instant composition.

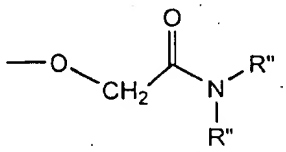
Transdermal delivery systems include patches, gels, tapes and creams, and can contain excipients such as solubilizers, permeation enhancers (e.g., fatty acids, fatty acid esters, fatty alcohols and amino acids), hydrophilic polymers (e.g., polycarbophil and polyvinylpyrolidone), and adhesives and tackifiers (e.g., polyisobutylenes, silicone-based adhesives, acrylates and polybutene).

The transdermal administration of folic acid can be facilitated by using the following ester form, which is hydrolyzed in vivo:



This ester can be a mono-ester (where either R or R' = H) or a di-ester (where neither R or R' is H). By way of example, R and R' can be independently selected from the following groups: lower alkyl from 1-8 carbons (e.g., methyl, ethyl, propyl and butyl); branched lower alkyl from 1-8 carbons (e.g., isopropyl, isobutyl and sec-butyl); cycloalkyl having 3-7 carbons (e.g., cyclopentyl and cyclohexyl); aryl (e.g., phenyl and substituted phenyl having 1-2 substitutients selected from lower alkyl and halo alkoxyl); and arylalkyl, where the alkyl is a straight or branched chain of 1-8 carbons, and aryl is a phenyl or substituted phenyl.

Glycolamide esters (both mono- and di-) can also be used for transdermal folic acid administration. Esters of this type are known to be useful as pro-drugs, and are cleaved rapidly in-vivo (J. Med. Chem. (1989) 32(3):727-34). In glycolamide esters, at least one of R or R' has the structure:



where (i) each R" is independently a lower alkyl (from 1-5 carbons) or, alternatively, (ii) both R" groups form an N-containing, 5-7-membered ring having 4-6 carbons.

Transmucosal delivery systems include patches, tablets, suppositories, pessaries, gels and creams, and can contain excipients such as solubilizers and enhancers (e.g., propylene glycol, bile salts and amino acids), and other vehicles (e.g., polyethylene glycol, fatty acid esters and derivatives, and hydrophilic polymers such as hydroxypropylmethylcellulose and hyaluronic acid).

Injectable drug delivery systems include solutions, suspensions, gels, microspheres and polymeric injectables, and can comprise excipients such as solubility-altering agents (e.g., ethanol, propylene glycol and sucrose) and polymers (e.g., polycaprylactones and PLGA's). Implantable systems include rods and discs, and can contain excipients such as PLGA and polycaprylactone.

Oral delivery systems include tablets and capsules. These can contain excipients such as binders (e.g., hydroxypropylmethylcellulose, polyvinyl pyrilodone, other cellulosic materials and starch), diluents (e.g., lactose and other sugars, starch, dicalcium phosphate and cellulosic materials), disintegrating agents (e.g., starch polymers and cellulosic materials) and lubricating agents (e.g., stearates and talc).

Solutions, suspensions and powders for reconstitutable delivery systems include vehicles such as suspending agents (e.g., gums, zanthans, cellulosics and sugars), humectants (e.g., sorbitol), solubilizers (e.g., ethanol, water, PEG and propylene glycol), surfactants (e.g., sodium lauryl sulfate, Spans, Tweens, and cetyl pyridine), preservatives and antioxidants (e.g., parabens, vitamins E and C, and ascorbic acid), anti-caking agents, coating agents, and chelating agents (e.g., EDTA).

Methods of determining therapeutically effective doses for administering the instant pharmaceutical composition in humans are known in the art. For example, these effective doses can readily be determined mathematically from the results of animal studies.

In one embodiment of the instant invention, the daily dose of folic acid administered to a subject according to the instant invention is from about 25 µg to about 1 g. Current recommendations in the art for daily folic acid dosages, upon which indication-specific dosages can readily be determined, include, for example: 50 µg/day (minimum effective dose, general population); 200 µg/day (recommended daily allowance, general

population); 400 µg/day (women of reproductive age); 800 µg/day (pregnant women); 500 µg/day (lactating women); 4 mg/day (women who have previously delivered a fetus having NTD); 1-5 mg/day (reduction of elevated homocysteine levels); and 200 µg/day (reduction of elevated plasma homocysteine levels in intermediate hyperhomocysteinemia patients).

The instant pharmaceutical compositions can be packaged in the form of pharmaceutical kits or packages in which the daily (or other periodic) dosages are arranged for proper sequential administration. Accordingly, this invention further provides a drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, each dosage unit comprising at least one of the instant pharmaceutical compositions.

This drug delivery system can be used to facilitate administering any of the various embodiments of the instant pharmaceutical compositions. In one embodiment, the system contains a plurality of dosages to be taken daily via oral administration (as commonly practiced in the oral contraceptive art). In another embodiment, the system contains a plurality of dosages to be administered weekly via transdermal administration (as commonly practiced in the hormone replacement art), thus providing continuous folic acid delivery.

For added convenience, the instant system can further comprise additional dosage units that contain folic acid, but no other active ingredient. Such delivery system could provide a total of 28 oral dosage

units, consistent with normal practice in the art of oral contraception. More specifically, an oral contraceptive delivery system could provide 21 daily dosage units, each comprising folic acid and oral contraceptive, and 7 additional dosage units comprising only folic acid and a suitable carrier. This type of system is consistent with the beneficial practice of daily, uninterrupted administration widely used with oral contraceptives.

This invention will be better understood by reference to the Examples which follow, but those skilled in the art will readily appreciate that the information detailed is only illustrative of the invention as described more fully in the claims which follow thereafter.

Example 1

Estrogen-Related Compounds

17-β-estradiol
Conjugated estrogens (including estrone sulfate, equilin, and 17-α-dihydroequilin)
Esterified estrogens
Estradiol
Estradiol valerate
Estriol
Estrone
Estrone sulfate
Estropipate
Ethinyl estradiol
Mestranol

Example 2

Selective Estrogen Receptor Modulators (SERMS)

Droloxifene
Idoxifene
Levormeloxifene
Raloxifene

Example 3

Progestin-Related Compounds

Available World-Wide
17-deacetyl norgestimate
Desogestrel
Ethynodiol diacetate
Levonorgestrel
Medroxyprogesterone acetate

Norethindrone
Norethindrone acetate
Norgestimate
Norgestrel
Progesterone

Available Outside the U.S.

3-keto desogestrel
Chlormadinone acetate
Cyproterone acetate
Dienogest
Dydrogesterone
Gestodene
Lynestrenol
Megestrol
Norethisterone
Norethisterone acetate
Norgestrienone
Quingestanol acetate

Example 4

Androgen-Related Compounds

Fluoxymesterone
Methyltestosterone
Testosterone
Testosterone enanthate

Example 5

Oral Contraceptives

Brand Name	Manufacturer**	ERC	PRC
DESOGEN	Organon	Ethinyl estradiol	Desogestrel
ORTHO CEPT	Ortho McNeil	Ethinyl estradiol	Desogestrel
DEMULEN 1/50	Searle	Ethinyl estradiol	Ethynodiol diacetate
ZOVIA 1/35	Watson	Ethinyl estradiol	Ethynodiol diacetate
DEMULEN 1/35	Searle	Ethinyl estradiol	Ethynodoil diacetate
ZOVIA 1/50	Watson	Ethinyl estradiol	Ethynodoil diacetate
LEVLEN	Berlex	Ethinyl estradiol	Levonorgestrel
TRI-LEVLEN	Berlex	Ethinyl estradiol	Levonorgestrel
LEVORA	Watson	Ethinyl estradiol	Levonorgestrel
ALESSE	Wyeth Ayerst	Ethinyl estradiol	Levonorgestrel
NORDETTE	Wyeth Ayerst	Ethinyl estradiol	Levonorgestrel
TRIPHASIL	Wyeth Ayerst	Ethinyl estradiol	Levonorgestrel
OVCON 35	Apothecon	Ethinyl estradiol	Norethindrone
OVCON 50	Apothecon	Ethinyl estradiol	Norethindrone
JENEST	Organon	Ethinyl estradiol	Norethindrone
ORTHO NOVUM 7/7/7	Ortho McNeil	Ethinyl estradiol	Norethindrone
ORTHO NOVUM 1/35	Ortho McNeil	Ethinyl estradiol	Norethindrone

Brand Name	Manufacturer	ERC	PRC
ORTHO NOVUM 1/50	Ortho McNeil	Mestranol	Norethindrone
ORTHO NOVUM 10-11	Ortho McNeil	Ethinyl estradiol	Norethindrone
NORETHIN 1/35E	Roberts	Ethinyl estradiol	Norethindrone
NORETHIN 1/50M	Roberts	Mestranol	Norethindrone
NORETHIN 1/35	Searle	Ethinyl estradiol	Norethindrone
NORETHIN 1/50	Searle	Mestranol	Norethindrone
BREVICON	Searle	Ethinyl estradiol	Norethindrone
NORINYL 1+35	Searle	Ethinyl estradiol	Norethindrone
NORINYL 1+50	Searle	Mestranol	Norethindrone
NOR-QD	Searle		Norethindrone
TRI-NORINYL	Searle	Ethinyl estradiol	Norethindrone
NELOVA 0.5/35	Warner Chilcott	Ethinyl estradiol	Norethindrone
NELOVA 1/35	Warner Chilcott	Ethinyl estradiol	Norethindrone
NELOVA 1/50	Warner Chilcott	Mestranol	Norethindrone
NELOVA 10/11	Warner Chilcott	Ethinyl estradiol	Norethindrone
NECON 0.5/35	Watson	Ethinyl estradiol	Norethindrone
NECON 1/35	Watson	Ethinyl estradiol	Norethindrone
NECON 1/50	Watson	Mestranol	Norethindrone
NECON 10/11	Watson	Ethinyl estradiol	Norethindrone
ESTROSTEP 21	Parke Davis	Ethinyl estradiol	Norethindrone acetate
ESTROSTEP Fe	Parke Davis	Ethinyl estradiol	Norethindrone acetate
LOESTRIN Fe 1.5/30	Parke Davis	Ethinyl estradiol	Norethindrone acetate

Brand Name	Manufacturer	ERC	PRC
LOESTRIN Fe 1/20	Parke Davis	Ethinyl estradiol	Norethindrone acetate
NORLESTRIN 1/50	Parke Davis	Ethinyl estradiol	Norethindrone acetate
NORLESTRIN 2.5/50	Parke Davis	Ethinyl estradiol	Norethindrone acetate
GENORA 1/35	Watson	Ethinyl estradiol	Norethisterone
GENORA 1/50	Watson	Mestranol	Norethisterone
GENORA 0.5/35	Watson	Ethinyl estradiol	Norethisterone
MICRONOR	Ortho McNeil		Norgestimate
ORTHO CYCLEN	Ortho McNeil	Ehinyl estradiol	Norgestimate
ORTHO TRI-CYCLEN	Ortho McNeil	Ethinyl estradiol	Norgestimate
LO/OVRAL	Wyeth Ayerst	Ethinyl estradiol	Norgestrel
OVRAL	Wyeth Ayerst	Ethinyl estradiol	Norgestrel
OVRETTE	Wyeth Ayerst		Norgestrel

** The manufacturers listed in this and other Examples are fully identified, by address, in Physicians' Desk Reference, 51st Ed. (1997) Medical Economics.

Example 6

Hormone Replacement Therapy
Vaginal Estrogen Preparations

Brand	ERC	Formulation
PREMARIN	Conj. Estrogens	Cream
ORTHO DIENOESTROL	Dienoestrol	Cream
OVESTIN	Estriol	Cream
ORTHO-GYNEST	Estriol	Pessary
TAMPOVAGAN	Stilbestrol	Pessary
ESTRING	Estradiol	Vaginal ring
VAGIFEM	Estradiol	Vaginal tablet

Example 7

Hormone Replacement Therapy
Transdermal Estrogen Preparations

Brand	ERC
ALORA	Estradiol
CLIMARA	Estradiol
DERMESTRIL	Estradiol
ESTRADERM	Estradiol
ESTRADERM TTS or MX	Estradiol
EVOREL	Estradiol
PEMATRIX	Estradiol
PEMPATCH	Estradiol
FEMSEVEN	Estradiol
MENOREST	Estradiol
PROGYNOVA TS	Estradiol
VIVELLE	Estradiol

Example 8

Hormone Replacement Therapy
Period-Free Therapy

Type	Brand	ERC	PRC
Continuous	CLIMESSE	Estradiol	Norethisterone
Combined therapy	EVORELCONTI	Estradiol	Norethisterone
	KLIOFEM	Estradiol	Norethisterone
	PREMIQUE	Conj. Estrogens	Medroxyprogesterone
	PREMPRO	Conj. Estrogens	Medroxyprogesterone acetate
Gonadomimetic	LIVIAL		

Example 9

Hormone Replacement Therapy
Estrogen Preparations

Brand	ERC	Formulation
ESTROGEL	Estradiol	Gel
SANDRENA	Estradiol	Gel
ESTRADIOL IMPLANT	Estradiol	Pellet implant
PREMARIN	Conjugated estrogens	Tablet
ESTRATAB	Esterified estrogens	Tablet
ESTRATEST ESTRATEST HS	Esterified estrogens Methyltestosterone	Tablet
MENEST	Esterified estrogens	Tablet
CLIMAGEST	Estradiol	Tablet
CLIMAVAL	Estradiol	Tablet
ELLESTE SOLO	Estradiol	Tablet
ESTRACE	Estradiol	Tablet
PROGYNOVA	Estradiol	Tablet
ZUMENON	Estradiol	Tablet
HORMONIN	Estradiol, estrone, estriol	Tablet
HARMOEN	Estrone	Tablet
OGEN	Estropipate	Tablet
ORTHO-EST	Estropipate	Tablet

Example 10

Combined Sequential Hormone Replacement Therapy

Type	Brand	ERC	PRC	Formul.
1/month	PREMIQUE CYCLE	Conj. Estrogens	Medroxy-progesterone	Tablet
	PREMPHASE	Conj. Estrogens	Medroxyproges-terone acetate	Tablet
	PREMPAK-C	Conj. Estrogens	Norgestrel	Tablet
	FEMPAK	Estradiol	Dydrogesterone	Tablet Patch
	FEMOSTON	Estradiol	Dydrogesterone	Tablet
	CYCLO-PROGYNOVA	Estradiol	Levonorgestrel	Tablet
	NUVELLE	Estradiol	Levonorgestrel	Tablet
	NUVELLE TS	Estradiol	Levonorgestrel	Patch
	CLIMAGEST	Estradiol	Norethisterone	Tablet
	ELLESTE DUET	Estradiol	Norethisterone	Tablet
	ESTRACOMBI	Estradiol	Norethisterone	Tablet Patches
	ESTRAPAK	Estradiol	Norethisterone	Tablet Patches
	EVOREL-PAK	Estradiol	Norethisterone	Tablet Patches
	EVORELSEQUI	Estradiol	Norethisterone	Tablet Patches
	TRISEQUENS	Estradiol, estriol	Norethisterone	Tablet
	IMPROVERA	Estrone	Medroxy-progesterone	Tablet
	MENOPHASE	Mestranol	Norethisterone	Tablet
1/qtr.	TRIDESTRA	Estradiol	Medroxy-progesterone	Tablet

Example 11

Hormone Replacement Therapy
Progestin-Only Formulations

Brand	PRC	Formulation
AMEN	Medroxyprogesterone acetate	Tablet
CYCRIN	Medroxyprogesterone acetate	Tablet
PROVERA	Medroxyprogesterone acetate	Tablet
AYGESTIN	Norethindrone acetate	Tablet

Example 12

Hormone Replacement Therapy
Androgenic Formulations

Brand Name	Manufacturer	Hormone Content
HALOTESTIN	Upjohn	Fluoxymesterone Oral
ANDROID	ICN	Methyltestosterone Oral
ORETON	ICN	Methyltestosterone Oral
TESTRED	ICN	Methyltestosterone Oral
DEPO-TESTOSTERONE	Upjohn	Testosterone cypionate Injectable
DELATESTRYL	BTG Pharmaceuticals	Testosterone enanthate Injectable
TESTODERM	Alza	Testosterone, USP Transdermal

Example 13

Formulation For Folic
Acid-Containing Oral Contraceptive

Ethinyl Estradiol (to deliver 35 μg)
Norethindrone (to deliver 1.0 mg)
Folic Acid (to deliver 400 μg)
Lactose, NF
Pregelatinized Starch, NF
Magnesium Stearate, NF

What is claimed is:

1. A pharmaceutical composition comprising (a) an oral contraceptive for preventing pregnancy in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the oral contraceptive is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

2. The pharmaceutical composition of claim 1, wherein the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

3. A pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a menopausal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

4. The pharmaceutical composition of claim 3, wherein the menopausal condition is a peri-menopausal condition.

5. The pharmaceutical composition of claim 3, wherein the menopausal condition is a post-menopausal condition.

6. The pharmaceutical composition of claim 3, wherein the disorder is selected from the group consisting of cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

7. A pharmaceutical composition comprising (a) a hormonal replacement composition for treating or preventing a hypogonadal condition in a subject, and (b) folic acid in an amount sufficient to treat or prevent a disorder which (i) afflicts subjects for whom the hormonal replacement composition is indicated at a higher-than-normal incidence, and (ii) is treatable or preventable by folic acid administration.

8. The pharmaceutical composition of claim 7, wherein the subject is female, and the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

9. The pharmaceutical composition of claim 7, wherein the subject is male, and the disorder is a cardiovascular disorder.

10. A method of administering folic acid to a subject for whom an oral contraceptive is indicated for preventing pregnancy, which comprises administering to the subject the pharmaceutical composition of claim 1, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

11. The method of claim 10, wherein the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

12. A method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a menopausal condition, which comprises administering to the subject the pharmaceutical composition of claim 3, wherein the subject is from a population whose members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

13. The method of claim 12, wherein the menopausal condition is a peri-menopausal condition.

14. The method of claim 12, wherein the menopausal condition is a post-menopausal condition.

15. The method of claim 12, wherein the disorder is selected from the group consisting of cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

16. A method of administering folic acid to a subject for whom a hormonal replacement composition is indicated for treating or preventing a hypogonadal condition, which comprises administering to the subject the pharmaceutical composition of claim 7, wherein the subject is from a population whose

members are afflicted with, or predisposed to become afflicted with, a disorder at a higher-than-normal incidence, the disorder being treatable or preventable by folic acid administration.

17. The method of claim 16, wherein the subject is female, and the disorder is selected from the group consisting of a teratogenic disorder, cervical dysplasia, a cervical carcinoma, and a cardiovascular disorder.

18. The method of claim 16, wherein the subject is male, and the disorder is a cardiovascular disorder.

19. A drug delivery system comprising a pharmaceutical package containing a plurality of dosage units, adapted for successive daily administration, wherein each dosage unit comprises a pharmaceutical composition selected from the group consisting of an oral contraceptive and a hormonal replacement composition.

20. The drug delivery system of claim 19, wherein each dosage unit comprises an oral contraceptive.